Immune System Module 1: Anatomy of the Lymphatic and Immune Systems
By the end of this section, you will be able to:

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroy **pathogens**. Pathogens are substances that can cause illness or death. The lymphatic system works together with the immune system so closely that they are usually studied together. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids from between the cells to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

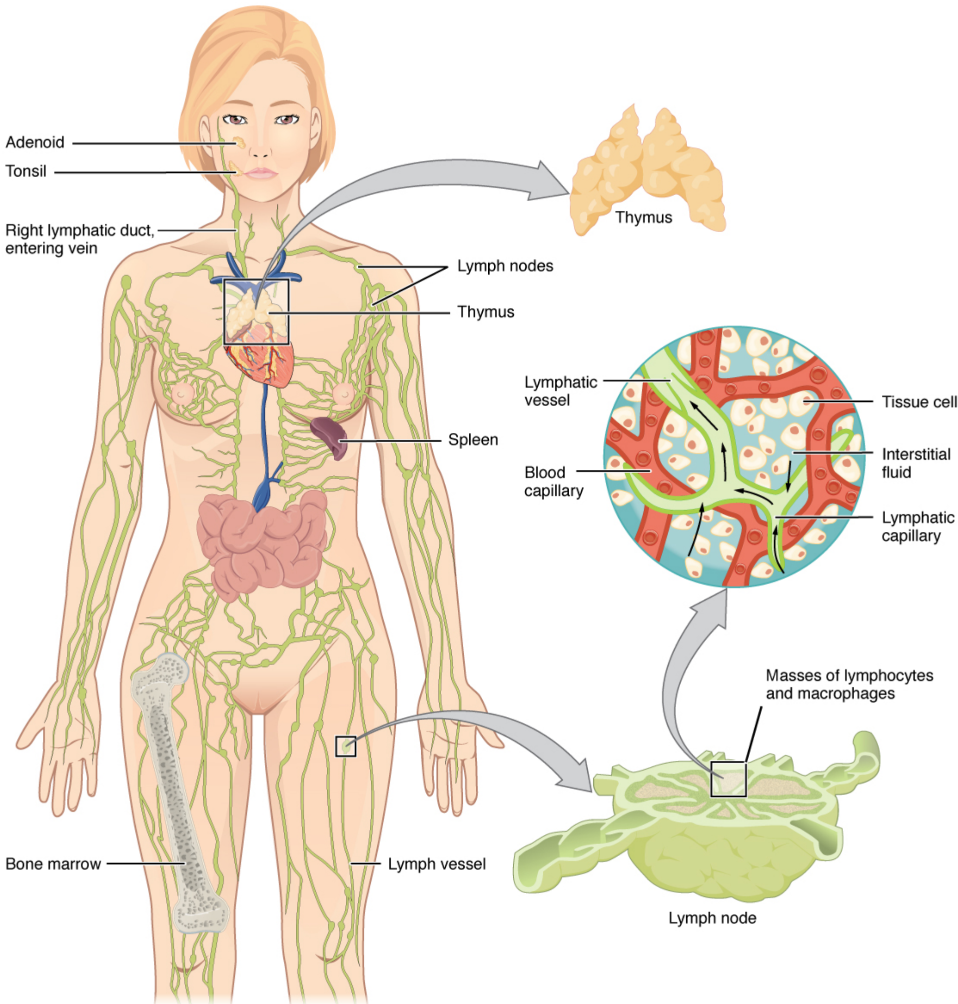
A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the spaces between the cells of the tissues each day. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as **interstitial fluid**. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, too much interstitial fluid accumulates in the tissue spaces. When too much fluid accumulates it

creates a condition called **lymphedema** which may lead to serious medical consequences.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located on the neck.
Anatomy of the Lymphatic System



Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

Lymphatic Capillaries

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary fats and fat-soluble vitamins to the bloodstream. These fats are abosorbed lacteals and form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the liver and then the bloodstream.

The Organization of Immune Function

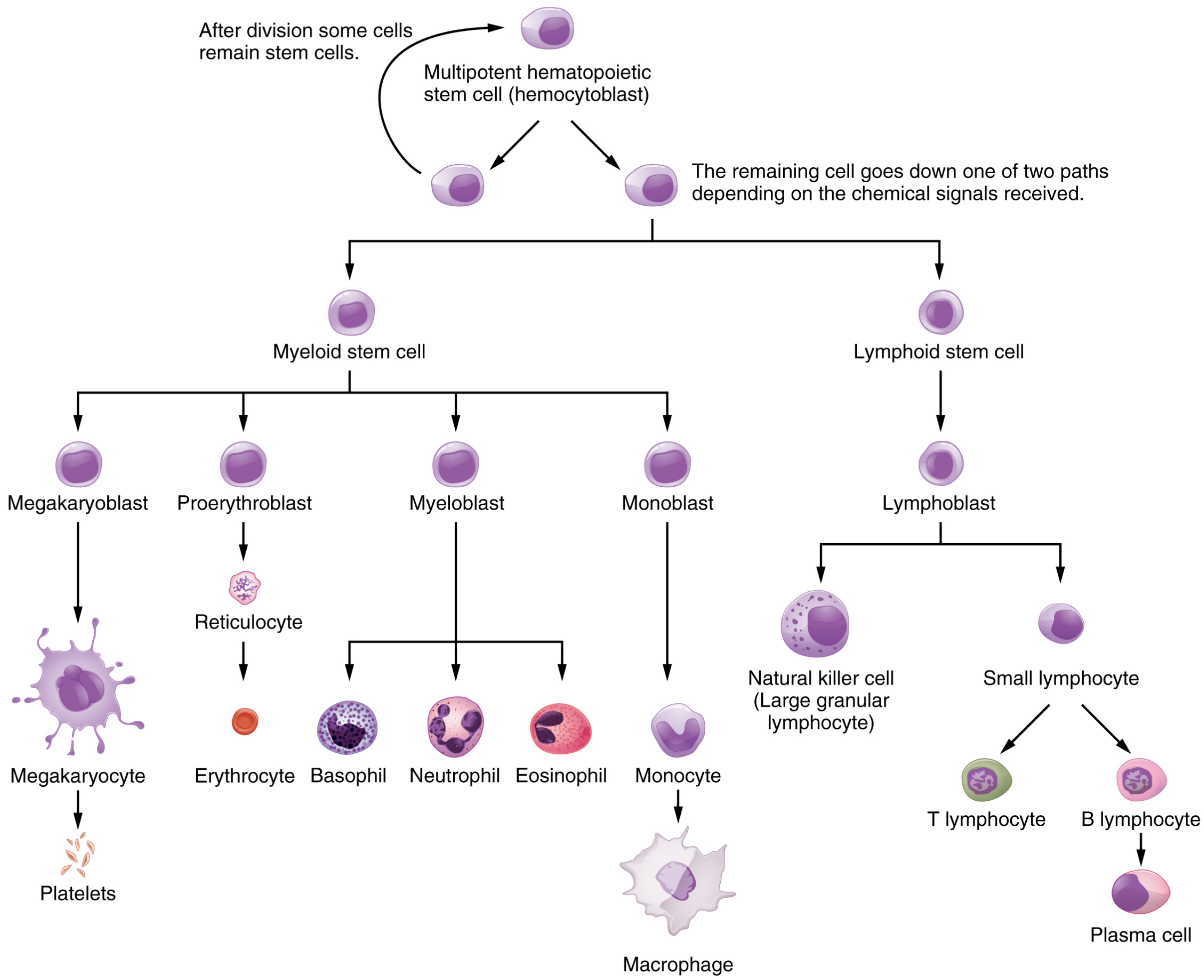
The immune system is a collection of barriers, cells, and proteins that interact and communicate with each other in extraordinarily complex ways to combat **pathogens**. A pathogen is anything that can make one sick when it enters the body. The modern model of immune function is organized into three phases based on the timing of their effects. The three phases consist of the following:

- **Barrier defenses** such as the skin are also referred to as mechanical defenses that act instantly to prevent pathogens from invading the body tissues.
- The rapid, but nonspecific **innate immune response**, consists of a variety of specialized cells and chemicals.
- The slower but more specific and effective **adaptive immune response**, involves many cell types and chemicals, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses.

The cells of the blood, including all those involved in the immune response are made in the bone marrow. **Hematopoietic** tissue contains stem cells that produce the blood cells. ([link]). Hematopoietic stem cells are present throughout adulthood to replace those lost to age or function. These cells produce the all the classes of white blood cells that are involved in the function of the the immune system. These cells can be divided into three classes based on function:

- **Phagocytic cells** also called phagocytes, ingest pathogens to destroy them
- **Lymphocytes** specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help regulate immune responses against parasites and viruses

Hematopoietic System of the Bone Marrow



All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses ([link]). The two basic types of lymphocytes, B cells and T cells, start out as identical cells with a large central nucleus surrounded by a thin layer of cytoplasm. As they develop they start to change and become distinguished from each other by their surface protein markers as well as by

the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-(think viruses, bacteria, etc.). An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells change into **plasma cells**.

T Cells

The **T cell**, on the other hand, does not secrete antibodies but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete substances that communicate with other cells of the adaptive immune system or destroy cells infected with pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

When a B cell discovers a pathogen, it creates plasma cells. When a signal from the B cell occurs the **plasma cell** creates the antibodies that attack the pathogen.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) chemicals. These chemicals destroy the invading cells, literally causing the cell membrane to burst. It shares this mechanism with the **cytotoxic T cells** of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.

Lymphocytes	
Type of lymphocyte	**Primary function**
B lymphocyte	Generates diverse antibodies
T lymphocyte	Secretes chemical messengers
Plasma cell	Secretes antibodies
NK cell	Destroys virally infected cells

Chapter Review

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are site in which mature lymphocytes congregate to mount immune responses. Many immune

system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Glossary

adaptive immune response
: relatively slow but very specific and effective immune response controlled by lymphocytes

afferent lymphatic vessels
: lead into a lymph node

antibody
: antigen-specific protein secreted by plasma cells; immunoglobulin

antigen
: molecule recognized by the receptors of B and T lymphocytes

barrier defenses
: antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

B cells
: lymphocytes that act by differentiating into an antibody-secreting plasma cell

bone marrow
: tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)
: lymphoid nodule associated with the respiratory tract

chyle
: lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli
: bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels
: lead out of a lymph node

germinal centers
: clusters of rapidly proliferating B cells found in secondary lymphoid tissues

high endothelial venules
: vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

immune system
: series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response
: rapid but relatively nonspecific immune response

lymph
: fluid contained within the lymphatic system

lymph node
: one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries
: smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system
: network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks
: large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes

white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules
unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)
lymphoid nodule associated with the mucosa

naïve lymphocyte
mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)
cytotoxic lymphocyte of innate immune response

plasma cell
differentiated B cell that is actively secreting antibody

primary lymphoid organ
site where lymphocytes mature and proliferate; red bone marrow and thymus gland

right lymphatic duct
drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs
sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen
secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell
lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and

cancer cells

thoracic duct
large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte
immature T cell found in the thymus

thymus
primary lymphoid organ; where T lymphocytes proliferate and mature

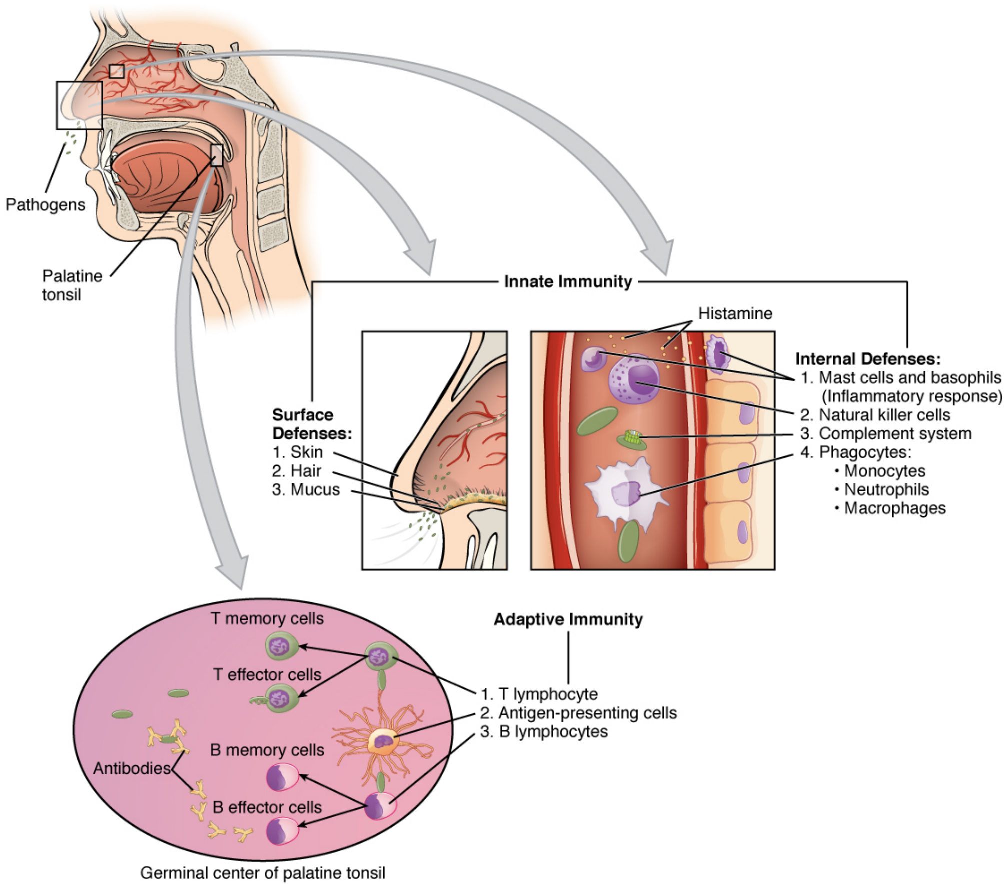
tonsils
lymphoid nodules associated with the nasopharynx

Module 2A & 2B: Barrier Defenses and the Innate Immune Response
By the end of this section, you will be able to:

- Describe the barrier defenses of the body
- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe various soluble factors that are part of the innate immune response
- Explain the steps of inflammation and how they lead to destruction of a pathogen
- Discuss early induced immune responses and their level of effectiveness

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the **innate immune response**, which is relatively rapid but nonspecific and thus not always effective, and the **adaptive immune response**, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens ([link]).

Cooperation between Innate and Adaptive Immune Responses



The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the **physical barriers** that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the body's tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter ([link]). The primary barrier to the entrance of microorganisms into the body is the **skin**. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria to grow, but as these cells are continuously dropped from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH and physically wash microbes away.

Barrier Defenses		
Site	**Specific defense**	**Protective aspect**
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH

Barrier Defenses		
Site	**Specific defense**	**Protective aspect**
Mucosal surfaces	Mucosal epithelium	Nonkeratinized epithelial cells
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

Another barrier is the **saliva** in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria. The acidic environment of the **stomach**, which is fatal to many pathogens, is also a barrier. Additionally, the **mucus layer** of the gastrointestinal tract, respiratory tract, reproductive tract, eyes (tears), ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, **ciliated epithelial cells** move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A **phagocyte** is a cell that is able to surround and ingest a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have gotten through the barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The **phagocyte takes the**

organism inside itself, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these cells and are therefore much more difficult to clear from the body. Macrophages and neutrophils, are the major phagocytes of the immune system.

A **macrophage** is an irregularly shaped phagocyte that is amoeboid (changes shape) and is the most useful of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls. They participate in innate immune responses. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense ([link]).

A **neutrophil** is a phagocytic cell that is attracted via chemical messenger from the bloodstream to infected tissues. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. The neutrophil is thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response.

A **monocyte** is a circulating cell that changes into a macrophage which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System			
Cell	**Cell type**	**Primary location**	**Function in the innate immune response**
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis
Neutrophil	Granulocyte	Blood	Phagocytosis

Phagocytic Cells of the Innate Immune System			
Cell	**Cell type**	**Primary location**	**Function in the innate immune response**
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell

Natural Killer Cells

Natural killer (NK) cells are a type of lymphocyte that have the ability to induce **apoptosis**, that is, cell death, in cells infected with pathogens such as bacteria and viruses. NK cells can induce apoptosis, in which a series of events inside the cell which causes the cell to self destruct. The cell programs its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals. The chemical is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins. A **perforin** is a protein that forms holes in the membranes of infected cells. This cause the cell to become leaky, losing important parts.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to reprooduce, no additional infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of specific pathogen molecules, such as bacterial cell wall components or bacterial proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a receptor that recognizes certain chemical features of a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and start phagocytosis or cellular apoptosis in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacteria and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular (between the cells) space, and the action of the cytokine induces the receiving cell to change in order to fight the pathogen. A **chemokine** is a chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Early induced Proteins

Early induced proteins are those that are not always present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of such proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium.

Complement System

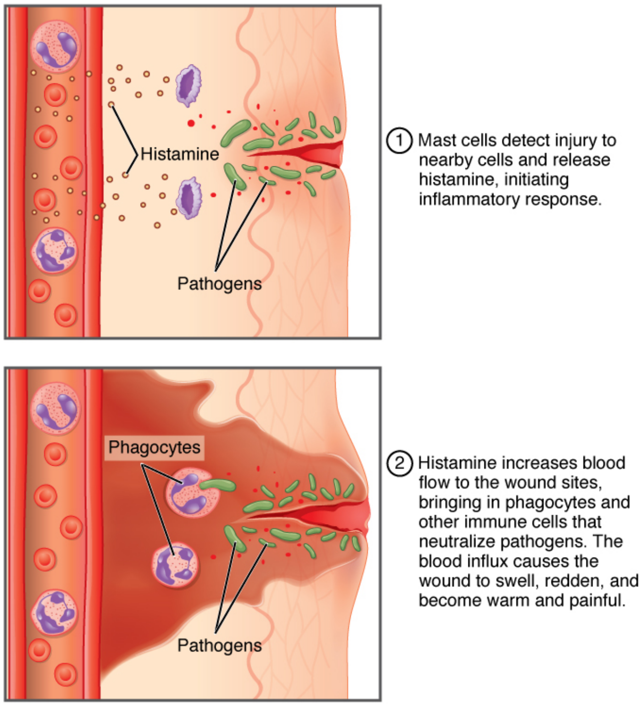
The **complement** system is a series of proteins always found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, Since they are always present. Made in the liver, they have a variety of functions in the innate immune response. Complement functions in the adaptive immune response in what is called the classical pathway. The complement system consists of several proteins that chemically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen labeling it for phagocytosis
- Move away from the pathogen and send chemical messages to other immune cells
- Form damaging pores (holes) in the plasma membrane of the pathogen

Protein from the complement system form the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic (water) balance. The MAC is especially effective against a broad range of bacteria. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by a chemical produced by complement.

Inflammatory Response

The most well known example of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling ("loss of function" is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in in the skin that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair ([link]).



This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. **Acute inflammation** is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and scarring. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- *Tissue Injury.* The released contents of injured cells stimulate the release of **mast cells** which in turn produce chemicals such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels, causing an increase in blood flow. Histamine also increases the amount of fluid that leaves the blood and flows into the damaged tissue and causes the swelling associated with inflammation.
  Additionally injured cells attract phagocytes, and basophils which are sources

of prostaglandins and leukotrienes. Leukotrienes attract neutrophils and increase blood vessel dialation (widening). Prostaglandins also cause vessel dilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.

- *Vasodilation.* Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability.* At the same time, inflammatory mediators increase the permeability of the local blood vessels, causing leakage of fluid into the space between the cells, resulting in the swelling, or **edema**, associated with inflammation.
- *Recruitment of Phagocytes.* Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemical messemger. Cytokines attract more macrophages which are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they take in the pathogens and die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally, interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is developed. In fact, both can cooperate and one can influence the other in their responses against pathogens.

Glossary

acute inflammation
: inflammation occurring for a limited time period; rapidly developing

chemokine
: soluble, long-range, cell-to-cell communication molecule

chronic inflammation
: inflammation occurring for long periods of time

complement
: enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine
: soluble, short-range, cell-to-cell communication molecule

early induced immune response
: includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand
: molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis

granzyme
: apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine
: vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation
: basic innate immune response characterized by heat, redness, pain, and swelling

interferons
: early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage
ameboid phagocyte found in several tissues throughout the body

mast cell
cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte
precursor to macrophages and dendritic cells seen in the blood

neutrophil
phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization
enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)
leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin
molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis
movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

Module 3: The Adaptive Immune Response: T lymphocytes and Their Functional Types
By the end of this section, you will be able to:

- Explain the advantages of the adaptive immune response over the innate immune response
- List the various characteristics of an antigen
- Describe the types of T cell antigen receptors
- Outline the steps of T cell development
- Describe the major T cell types and their functions

Innate immune responses often ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The **specificity** of the adaptive immune response—its ability to specifically recognize and make a strong response against a wide variety of pathogens—is its great strength. Antigens, are the small chemical groups attached to pathogens. They are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as 10^{11}, or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics.

Primary Disease and Immunological Memory

The immune system’s first exposure to a pathogen is called a **primary (adaptive) response**. Symptoms of a first infection from a particular pathogen, called the primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster that the primary response. The **secondary adaptive response** often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of **immunological memory**, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual’s exposure to pathogens early in life spares the person from these diseases later in life.

Self Recognition

A third important feature of the adaptive immune response is its ability to distinguish between **self-antigens** , those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, they "learn" to recognize self-antigen, preventing a damaging immune response against the body. These mechanisms are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

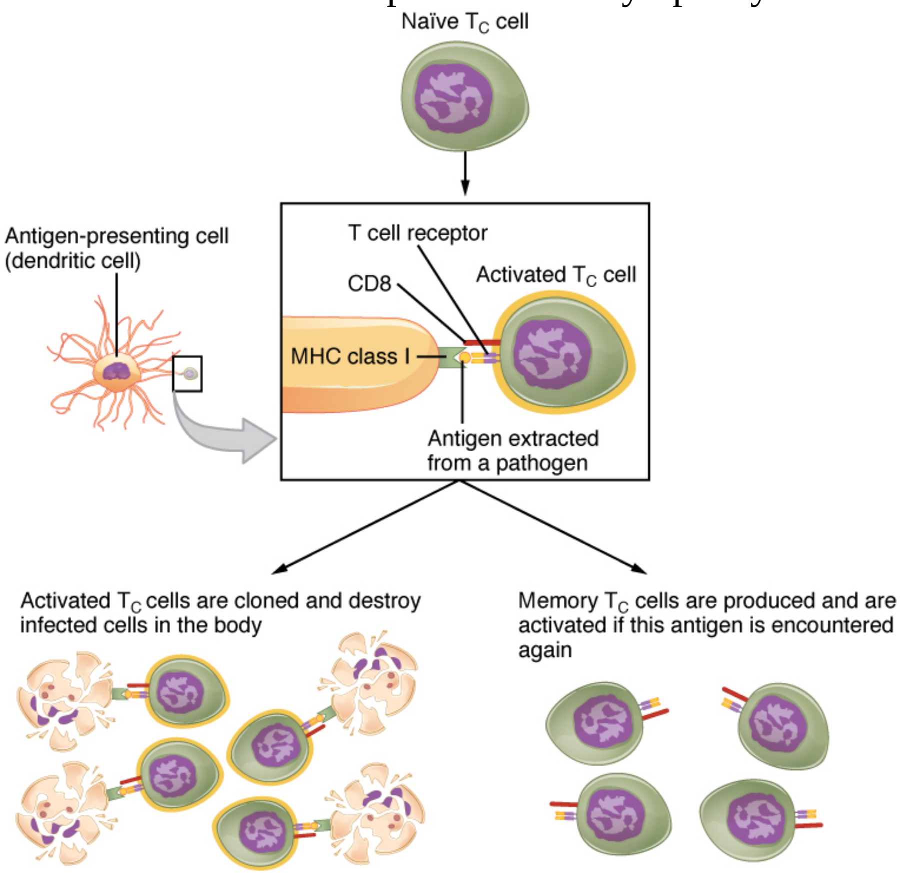
T Cell-Mediated Immune Responses

The primary cells that control the adaptive immune response are the lymphocytes, **the T and B cells** . T cells are particularly important, as they not only control a multitude of immune responses directly, but also control B cell immune responses in many cases. Thus, many of the decisions about how to attack a pathogen are made at the T cell level, so knowledge of their functional types is crucial to understanding the adaptive immune responses as a whole.

Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing a foreign antigen "presented" by a **major histocompatibility complex or MHC** molecule and begin dividing rapidly by mitosis. This increase of T cells is called **clonal expansion** and is necessary to make the immune response strong enough to effectively control a pathogen. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection (see [link]).

Clonal Selection and Expansion of T Lymphocytes



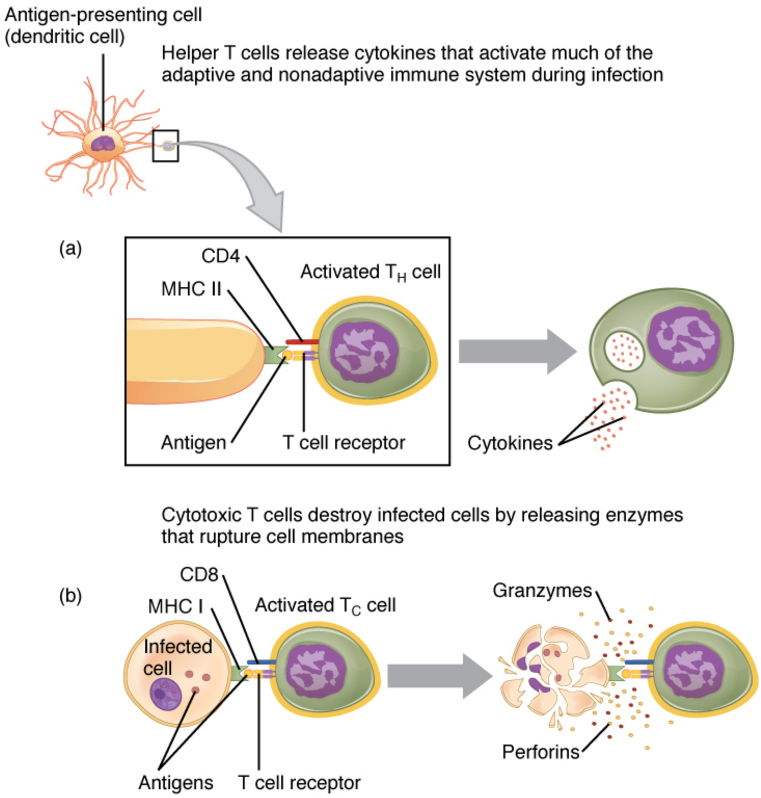
Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

The Cellular Basis of Immunological Memory

As already discussed, one of the major features of an adaptive immune response is the development of immunological memory. During a primary adaptive immune response, both **memory T cells** and **effector T cells** are generated. Memory T cells are long-lived and can even persist for a lifetime. Memory cells are primed to act rapidly. Thus, any additional exposure to the pathogen will begin a very rapid T cell response. This rapid, secondary adaptive response generates large numbers of effector T cells so fast that the pathogen is often overwhelmed before it can cause any symptoms of disease. This is what is meant by immunity to a disease. The same pattern of primary and secondary immune responses occurs in B cells and the antibody response, as will be discussed later in the chapter.

T Cell Types and their Functions

In the discussion of T cell development, you saw that mature T cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T cell in close contact with the antigen-presenting cell by directly binding to the MHC molecule (to a different part of the molecule than does the antigen). Thus, T cells and antigen-presenting cells are held together in two ways: by CD4 or CD8 attaching to MHC and by the T cell receptor binding to antigen ([link]).
Pathogen Presentation



(a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by a class I MHC molecule, and CD8 interacts with it.

Helper T Cells and their Cytokines

Helper T cells (Th) function by secreting cytokines that act to enhance other immune responses. These cytokine chemicals signal the T and B cells

that a pathogen is present. Essentially a helper T cell "turns on" the rest of the B and T cells. Th cells act on B cells to to stimulate the production of plasma cells, which make antibodies.

Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells in the same way as natural killer cells. They release chemicals that cause a cell to self destruct. Tc cells work by killing an infected cell before the pathogen can reproduce. Tc cells are developed during an immune response by destructing the infected cells, they overwhelm the ability of the pathogen to cause disease. In addition, each Tc cell can kill more than one target cell making them especially effective.

Regulatory T Cells

Suppressor T cells, suppress other T cell immune responses. They stifle (stop) other T cell immune responses. This is an important feature of the immune response. If immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on and the types of pathogens they work against (see [link]).

Chapter Review

T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface. They do not recognize self-antigens, however, but only processed antigen presented on their surfaces in a binding groove of a major histocompatibility complex molecule. T cells develop in the thymus, where they learn to use self-MHC molecules to

recognize only foreign antigens, thus making them tolerant to self-antigens. There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.

Glossary

antigenic determinant
: (also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

antigen presentation
: binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule

antigen processing
: internalization and digestion of antigen in an antigen-presenting cell

antigen receptor
: two-chain receptor by which lymphocytes recognize antigen

clone
: group of lymphocytes sharing the same antigen receptor

clonal expansion
: growth of a clone of selected lymphocytes

clonal selection
: stimulating growth of lymphocytes that have specific receptors

constant region domain
: part of a lymphocyte antigen receptor that does not vary much between different receptor types

cytotoxic T cells (Tc)
: T lymphocytes with the ability to induce apoptosis in target cells

effector T cells
: immune cells with a direct, adverse effect on a pathogen

helper T cells (Th)
T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

immunological memory
ability of the adaptive immune response to mount a stronger and faster immune response upon re-exposure to a pathogen

major histocompatibility complex (MHC)
gene cluster whose proteins present antigens to T cells

memory T cells
long-lived immune cell reserved for future exposure to an pathogen

MHC class I
found on most cells of the body, it binds to the CD8 molecule on T cells

MHC class II
found on macrophages, dendritic cells, and B cells, it binds to CD4 molecules on T cells

negative selection
selection against thymocytes in the thymus that react with self-antigen

polyclonal response
response by multiple clones to a complex antigen with many determinants

primary adaptive response
immune system’s response to the first exposure to a pathogen

positive selection
selection of thymocytes within the thymus that interact with self, but not non-self, MHC molecules

regulatory T cells (Treg)

(also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

secondary adaptive response
: immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

T cell tolerance
: process during T cell differentiation where most T cells that recognize antigens from one’s own body are destroyed

Th1 cells
: cells that secrete cytokines that enhance the activity of macrophages and other cells

Th2 cells
: cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

variable region domain
: part of a lymphocyte antigen receptor that varies considerably between different receptor types

Immune System Module 4: The Adaptive Immune Response: B-lymphocytes and Antibodies
By the end of this section, you will be able to:

- Explain how B cells mature and how B cell tolerance develops
- Discuss how B cells are activated and differentiate into plasma cells
- Describe the structure of the antibody classes and their functions

Antibodies were the first part of the adaptive immune response to be discovered by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-infection with the same pathogen. Early microbiologists took blood from a patient who was already exposed to a certain pathogen and tested it. They learned that there was a substance in the blood, called an **antibody** which prevented the individual from getting sick from that pathogen. As studies continued, it was discovered that antibodies prevented the person from getting sick with the same illness a second time.

What is an antibody? An antibody protein is essentially a secreted from a plasma cell. which develops from B cell. There are five different classes of antibodies found in humans: IgM, IgD, IgG, IgA, and IgE. Each of these has specific functions in the immune response. As researchers learn about them, they are able to learn about the great variety of antibody functions critical to many adaptive immune responses.

B Cell Differentiation and Activation

B cells differentiate in the bone marrow. During the process of maturation, up to 100 trillion different clones of B cells are generated, which is similar to the diversity of antigen receptors seen in T cells.

B cells are activated by binding to antigen. They differentiate into plasma cells. Plasma cells often leave the lymphoid organs migrate back to the bone marrow, where the whole differentiation process started. After secreting antibodies for a specific period, the B cells die, as most of their energy is devoted to making antibodies and not to maintaining themselves.

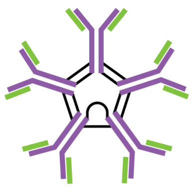
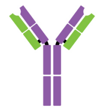
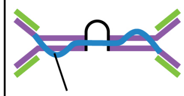
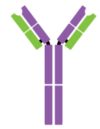
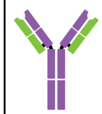
The final B cell is the **memory B cell**, which results from exposure to a specific pathogen. Memory B cells function in a way similar to memory T cells. They lead to a stronger and faster secondary response when compared to the primary response. They "remember" the antibody for that pathogen which leads to quick production of antibodies. Often you do not experience any symptoms as the secondary response is so quick and effective.

Antibody Structure

Antibodies are proteins consisting of two chains with attached carbohydrates. The **heavy chain** and the **light chain** are the two proteins that form the antibody. The main differences between the classes of antibodies are in the differences between their heavy chains. There are 2 regions of the heavy chains known as the **constant and variable regions**.

Five Classes of Antibodies and their Functions

Five Classes of Antibodies

The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

IgM is the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its large shape allows it to bind well to many bacterial surfaces.Thus, it is a very effective antibody against bacteria at early stages of a primary antibody response.

IgG is the main antibody of secondary responses in the blood. IgG is an antibody that clears pathogens from the blood and can activate complement proteins. This class of antibody is the one that crosses the placenta to protect the developing fetus from disease.

IgA exists in exocrine gland secretions of the mucous membranes, including mucus, saliva, and tears. Thus, IgA is the only antibody to leave the interior of the body to protect body surfaces. IgA is also of importance to newborns, because this antibody is present in mother’s breast milk (colostrum), which serves to protect the infant from disease.

IgE is usually associated with allergies and anaphylaxis. It is present in the lowest concentration in the blood. IgE is very specific, such that if a person is allergic to peanuts, there will be peanut-specific IgE bound to his or her cells. In this person, eating peanuts will have a severe allergic reactions, including **anaphylaxis**, a severe, systemic allergic response that can cause death.

IgD signals the B cells to be activated. By being activated, they are ready to take part in the defense of the body in the immune system. IgD also plays a role in protecting our respiratory systems from bacteria.

Active versus Passive Immunity

Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by (1) the active development of an immune response in the infected individual or (2) the passive transfer of immune components from an immune individual to a nonimmune one. Both active and passive immunity have examples in the natural world and as part of medicine.

Active immunity is the resistance to pathogens acquired during an adaptive immune response within an individual. ([link]) More simply, active immunity occurs when you make your own antibodies. **Naturally acquired active immunity** , is the response to a pathogen which has invaded one's body that leads to the manufacture of antibodies. **Artificially acquired active immunity** involves the use of vaccines. A vaccine is a killed or weakened pathogen that, when administered to a healthy individual, leads to the development of antibodies without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from antibodies. Although you make your own antibodies, a vaccine is considered to be artificial immunity since it needs to be administered to you. The discovery of vaccines was one of the major medical advances of the twentieth century and led to the wipe out of smallpox and the control of many infectious diseases, including polio, measles, and whooping cough.

Active versus Passive Immunity		
	Natural	**Artificial**
Active	Adaptive immune response	Vaccine response
Passive	Trans-placental antibodies/breastfeeding	Immune globulin injections

Passive immunity arises from the transfer of antibodies to an individual without requiring them to create their own antibodies. **Naturally acquired passive immunity** is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life. A newborn benefits from the IgA antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the antibodies of the mother to the pathogens to which she has been exposed. In medicine, **artificially acquired passive immunity** usually involves injections of immunoglobulins, taken from people or animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen. The downside to both types of passive immunity is the lack of ability to create their own antibodies. Once the antibodies are transferred, they are effective for only a limited time before they degrade. Once again an example such as breastfeeding is natural immunity, since it happens without medical administration. Immunoglobulins are considered artificial immunity since they have to be administered.

Exercise:

Problem:

Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

Solution:

Breastfeeding is an example of natural immunity acquired passively.

Glossary

active immunity
: immunity developed from an individual's own immune system

central tolerance
: B cell tolerance induced in immature B cells of the bone marrow

class switching
: ability of B cells to change the class of antibody they produce without altering the specificity for antigen

clonal anergy
: process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional

clonal deletion
: removal of self-reactive B cells by inducing apoptosis

Fc region
: in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules

heavy chain
: larger protein chain of an antibody

IgA
: antibody whose dimer is secreted by exocrine glands, is especially effective against digestive and respiratory pathogens, and can pass immunity to an infant through breastfeeding

IgD
: class of antibody whose only known function is as a receptor on naive B cells; important in B cell activation

IgE
: antibody that binds to mast cells and causes antigen-specific degranulation during an allergic response

IgG
: main blood antibody of late primary and early secondary responses; passed from mother to unborn child via placenta

IgM
: antibody whose monomer is a surface receptor of naive B cells; the pentamer is the first antibody made blood plasma during primary responses

immunoglobulin
: protein antibody; occurs as one of five main classes

light chain
: small protein chain of an antibody

passive immunity
: transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

peripheral tolerance
: mature B cell made tolerant by lack of T cell help

T cell-dependent antigen
: antigen that binds to B cells, which requires signals from T cells to make antibody

T cell-independent antigen
: binds to B cells, which do not require signals from T cells to make antibody

Immune System Module 5: The Immune Response against Pathogens

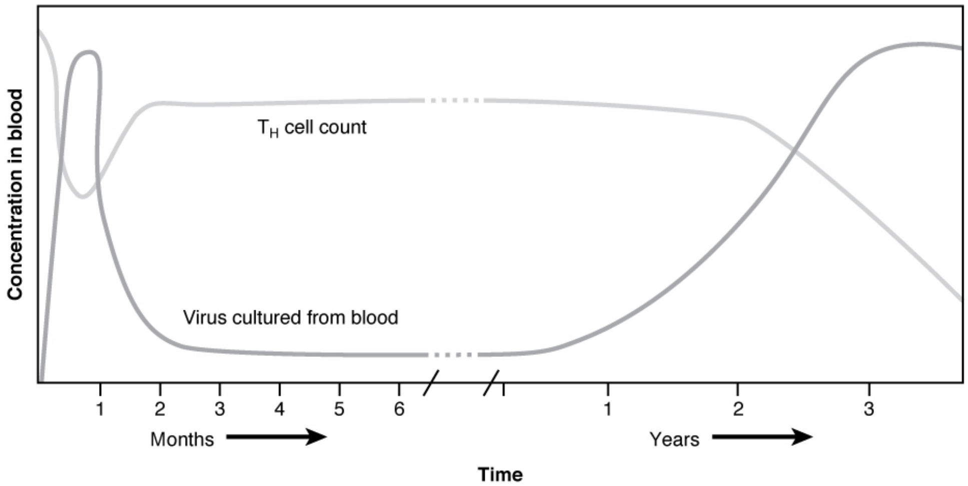
By the end of this section, you will be able to:

- Explain the development of immunological competence
- Describe the mucosal immune response
- Discuss immune responses against bacterial, viral, fungal, and animal pathogens
- Describe different ways pathogens evade immune responses

Now that you understand the development of B cells and T cells, and some of their major functions, how do all of these various cells, proteins, and cytokines come together to actually resolve an infection? Ideally, the immune response will rid the body of a pathogen entirely. The adaptive immune response is well suited to this purpose. Think of a primary infection as a race between the pathogen and the immune system. The pathogen bypasses barrier defenses and starts multiplying in the host's body. During the first 4 to 5 days, the innate immune response will partially control, but not stop, pathogen growth. As the adaptive immune response gears up, however, it will begin to clear the pathogen from the body, while at the same time becoming stronger and stronger. As the antibody levels rise, the virus levels decline, and this is a sign that the immune response is being at least partially effective.

An excellent example of this is seen in a patient with HIV disease ([link]). Notice that antibodies are made early in this disease, and the increase in anti-HIV antibodies correlates with a decrease in detectable virus in the blood. Although these antibodies are an important marker for diagnosing the disease, they are not sufficient to completely clear the virus. Several years later, the vast majority of these individuals, if untreated, will lose their entire adaptive immune response, including the ability to make antibodies, during the final stages of AIDS.

HIV Disease Progression



Seroconversion, the rise of anti-HIV antibody levels and the concomitant decline in measurable virus levels, happens during the first several months of HIV disease. Unfortunately, this antibody response is ineffective at controlling the disease, as seen by the progression of the disease towards AIDS, in which all adaptive immune responses are compromised.

Note:

Everyday Connection

Disinfectants: Fighting the Good Fight?

“Wash your hands!” Parents have been telling their children this for generations. Dirty hands can spread disease. But is it possible to get rid of enough pathogens that children will never get sick? Are children who avoid exposure to pathogens better off? The answers to both these questions appears to be no.

Antibacterial wipes, soaps, gels, and even toys with antibacterial substances embedded in their plastic are ubiquitous in our society. Still, these products do not rid the skin and gastrointestinal tract of bacteria, and it would be harmful to our health if they did. We need these nonpathogenic bacteria on and within our bodies to keep the pathogenic ones from growing. The urge to keep children perfectly clean is thus probably

misguided. Children will get sick anyway, and the later benefits of immunological memory far outweigh the minor discomforts of most childhood diseases. In fact, getting diseases such as chickenpox or measles later in life is much harder on the adult and are associated with symptoms significantly worse than those seen in the childhood illnesses. Of course, vaccinations help children avoid some illnesses, but there are so many pathogens, we will never be immune to them all.

Could over-cleanliness be the reason that allergies are increasing in more developed countries? Some scientists think so. **Allergies** are based on an IgE antibody response. An allergy is an error of the immune system. The body interprets a harmless protein as an antigen and fights against it, despite the fact that the substance poses no threat to the individual. Many scientists think the system evolved to help the body rid itself of worm parasites. The hygiene theory is the idea that the immune system is geared to respond to antigens, and if pathogens are not present, it will respond instead to inappropriate antigens such as allergens and self-antigens. This is one explanation for the rising incidence of allergies in developed countries, where the response to nonpathogens like pollen, shrimp, and cat dander cause allergic responses while not serving any protective function.

Autoimmune diseases like lupus and rheumatoid arthritis are caused by the immune system's attack on proteins manufactured by one's own body. Again these "self" substance pose no threat to the individual but the immune system mistakenly attacks them.

Defenses against Viruses

The primary mechanisms against viruses are NK cells, interferons, and cytotoxic T cells. Antibodies are effective against viruses mostly during a secondary response, where an immune individual can neutralize them based on a previous exposure. Antibodies have no effect on viruses once they enter the cell, since antibodies are not able to penetrate the plasma membrane of the cell.

Interferons have activity in slowing viral replication and are used in the treatment of certain viral diseases, such as hepatitis B and C, but their

ability to eliminate the virus completely is limited. The cytotoxic T cell response, though, is key, as it eventually overwhelms the virus and kills infected cells before the virus can complete its replication cycle. The ability of cytotoxic T cells to kill more than one target cell make these cells especially effective against viruses. In fact, without cytotoxic T cells, it is likely that humans would all die at some point from a viral infection (if no vaccine were available).

Chapter Review

Early childhood is a time when the body develops much of its immunological memory that protects it from diseases in adulthood. The components of the immune response that have the maximum effectiveness against a pathogen are often associated with the class of pathogen involved. Bacteria and fungi are especially susceptible to damage by complement proteins, whereas viruses are taken care of by interferons and cytotoxic T cells. Worms are attacked by eosinophils. Pathogens have shown the ability, however, to evade the body's immune responses, some leading to chronic infections or even death. The immune system and pathogens are in a slow, evolutionary race to see who stays on top. Modern medicine, hopefully, will keep the results skewed in humans' favor.

Glossary

macrophage oxidative metabolism
: metabolism turned on in macrophages by T cell signals that help destroy intracellular bacteria

neutralization
: inactivation of a virus by the binding of specific antibody

seroconversion
: clearance of pathogen in the serum and the simultaneous rise of serum antibody

Immune System Module 6: Transplantation and Cancer Immunology
By the end of this section, you will be able to:

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. **Tissue typing** is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.

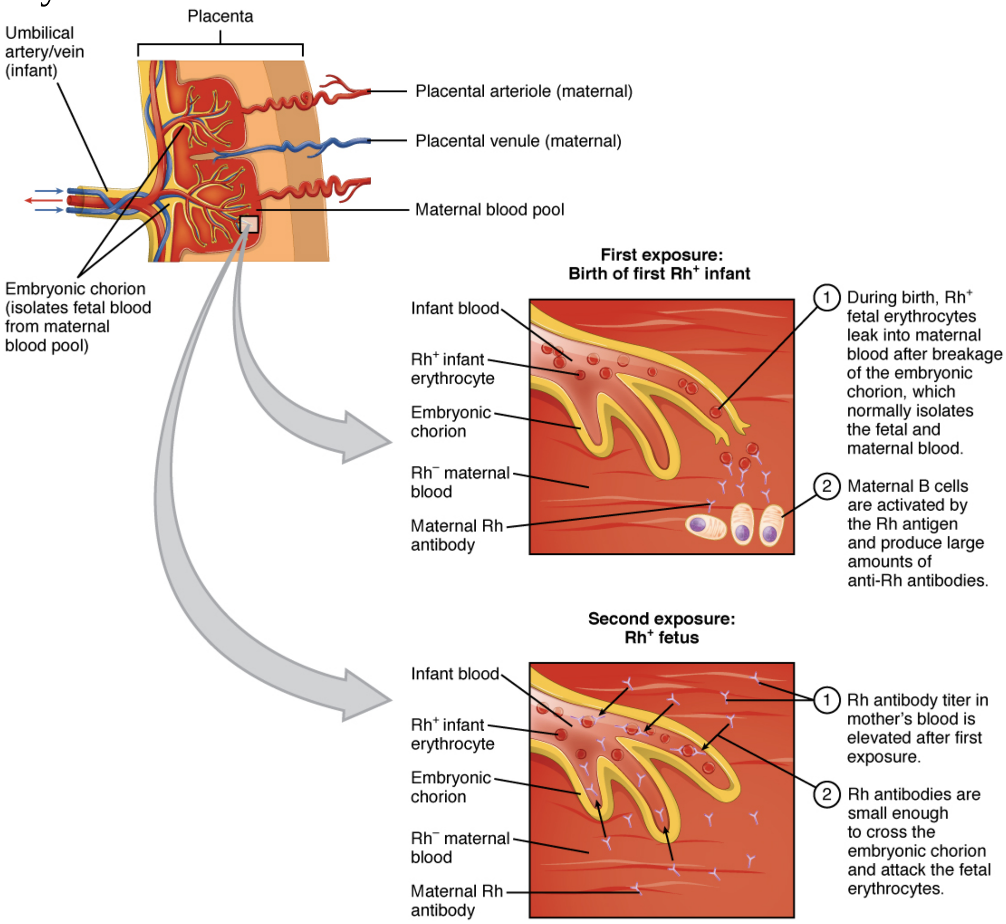
The Rh Factor

Red blood cells can be typed based on their surface antigens. ABO blood type, in which individuals are type A, B, AB, or O according to their genetics, is one example. A separate antigen system seen on red blood cells is the Rh antigen. When someone is “A positive” for example, the positive refers to the presence of the Rh antigen, whereas someone who is “A negative” would lack this molecule.

An interesting consequence of Rh factor expression is seen in **erythroblastosis fetalis**, a hemolytic disease of the newborn ([link]). This disease occurs when mothers negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the mother makes a primary anti-Rh antibody response to the fetal blood cells that enter the maternal bloodstream. If the mother has a second Rh-positive child, IgG antibodies against Rh-positive blood mounted during this

secondary response cross the placenta and attack the fetal blood, causing anemia. This is a consequence of the fact that the fetus is not genetically identical to the mother, and thus the mother is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the mother during the subsequent births, destroying any fetal blood that might enter her system and preventing the immune response.

Erythroblastosis Fetalis



Erythroblastosis fetalis (hemolytic disease of the newborn) is the result of an immune response in an Rh-negative mother who has multiple children with an Rh-positive father. During the first birth, fetal blood enters the mother's circulatory system, and anti-Rh antibodies are made. During the gestation of the second child, these antibodies cross the placenta and attack the blood of the fetus. The treatment for this disease is to give the mother

anti-Rh antibodies (RhoGAM) during the first pregnancy to destroy Rh-positive fetal red blood cells from entering her system and causing the anti-Rh antibody response in the first place.

Tissue Transplantation

When a donor organ expresses molecules that are different from the recipient, the latter will often mount a cytotoxic T cell response to the organ and reject it. If a biopsy of a transplanted organ exhibits a massive invasion of T lymphocytes within the first weeks after transplant, it is a sign that the transplant is likely to fail. The response is a classical, and very specific, primary T cell immune response. As far as medicine is concerned, the immune response in this scenario does the patient no good at all and causes significant harm.

Immunosuppressive drugs such as cyclosporine A have made transplants more successful. A successful transplant usually requires a match between at least 3–4 protein molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to have identical protein molecules than unrelated individuals do. In fact, due to the extensive variety in these molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

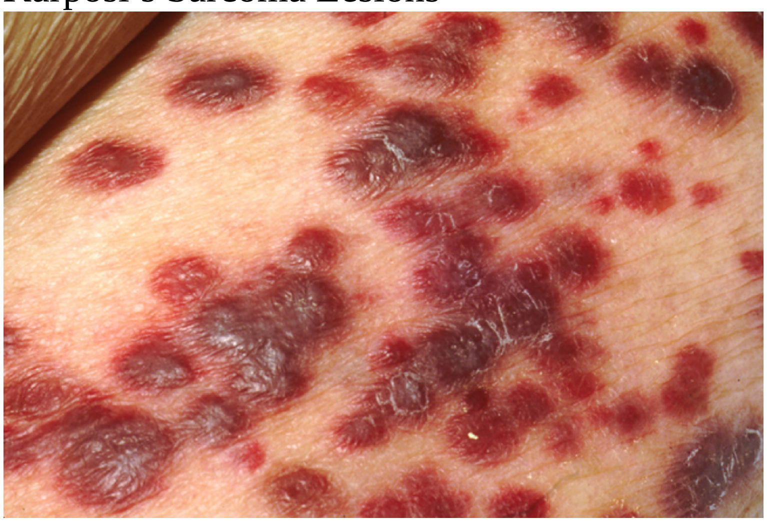
One disease of transplantation occurs with bone marrow transplants, which are used to treat various diseases such leukemia. Because the bone marrow cells being transplanted contain lymphocytes capable of mounting an immune response, and because the recipient’s immune response has been destroyed before receiving the transplant, the donor cells may attack the recipient tissues, causing **graft-versus-host disease**. Symptoms of this disease, which usually include a rash and damage to the liver and mucosa, are variable, and attempts have been made to moderate the disease by first

removing mature T cells from the donor bone marrow before transplanting it.

Immune Responses Against Cancer

It is clear that with some cancers, for example Kaposi's sarcoma, a healthy immune system does a good job at controlling them ([link]). This disease, which is caused by the human herpesvirus, is almost never observed in individuals with strong immune systems, such as the young and **immunocompetent**. Being immunocompetent means having a healthy immune response. Some cancers that are caused by viruses include liver cancer caused by the hepatitis B virus and cervical cancer caused by the human papilloma virus. As these last two viruses have vaccines available for them, getting vaccinated can help prevent these two types of cancer by stimulating the immune response.

Karposi's Sarcoma Lesions



(credit: National Cancer Institute)

It is tempting to focus on the complexity of the immune system and the problems it causes as a negative. The upside to immunity, however, is so much greater: The benefit of staying alive far outweighs the negatives caused when the system does sometimes go awry. Working on "autopilot," the immune system helps to maintain your health and kill pathogens. The

only time you really miss the immune response is when it is not being effective and illness results, or, as in the extreme case of HIV disease, the immune system is gone completely.

Note:
Everyday Connection
One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception ([link]).

Effects of Stress on Body Systems

System	Stress-related illness
Integumentary system	Acne, skin rashes, irritation
Nervous system	Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance

Effects of Stress on Body Systems	
System	**Stress-related illness**
Muscular and skeletal systems	Muscle and joint pain, neck and shoulder pain
Circulatory system	Increased heart rate, hypertension, increased probability of heart attacks
Digestive system	Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss
Immune system	Depressed ability to fight infections
Male reproductive system	Lowered sperm production, impotence, reduced sexual desire
Female reproductive system	Irregular menstrual cycle, reduced sexual desire

At one time, it was assumed that all types of stress reduced all aspects of the immune response, but the last few decades of research have painted a different picture. First, most short-term stress does not impair the immune system in healthy individuals enough to lead to a greater incidence of diseases. However, older individuals and those with suppressed immune responses due to disease or immunosuppressive drugs may respond even to short-term stressors by getting sicker more often. It has been found that short-term stress diverts the body's resources towards enhancing innate immune responses, which have the ability to act fast and would seem to help the body prepare better for possible infections associated with the trauma that may result from a fight-or-flight exchange. The diverting of

resources away from the adaptive immune response, however, causes its own share of problems in fighting disease.

Chronic stress, unlike short-term stress, may inhibit immune responses even in otherwise healthy adults. The suppression of both innate and adaptive immune responses is clearly associated with increases in some diseases, as seen when individuals lose a spouse or have other long-term stresses, such as taking care of a spouse with a fatal disease or dementia. The new science of psychoneuroimmunology, while still in its relative infancy, has great potential to make exciting advances in our understanding of how the nervous, endocrine, and immune systems have evolved together and communicate with each other.

Chapter Review

Blood transfusion and organ transplantation both require an understanding of the immune response to prevent medical complications. Blood needs to be typed so that natural antibodies against mismatched blood will not destroy it, causing more harm than good to the recipient. Transplanted organs must be matched by their MHC molecules and, with the use of immunosuppressive drugs, can be successful even if an exact tissue match cannot be made. Another aspect to the immune response is its ability to control and eradicate cancer. Although this has been shown to occur with some rare cancers and those caused by known viruses, the normal immune response to most cancers is not sufficient to control cancer growth. Thus, cancer vaccines designed to enhance these immune responses show promise for certain types of cancer.

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Glossary

erythroblastosis fetalis
: disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood

graft-versus-host disease
: in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

MHC polygeny
: multiple MHC genes and their proteins found in body cells

MHC polymorphism
: multiple alleles for each individual MHC locus

psychoneuroimmunology
: study of the connections between the immune, nervous, and endocrine systems

tissue typing
: typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure